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FILTERABLE FORMS OF MICROORGANISMS AND THEIR CONNECTION WITH VIRUSES

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[According to the Russian editor's note, the article summarized below forms a part of the discussion on noncellular forms of microorganisms which has been conducted in Mikrobiologiya for some time. The editor adds that no further articles will be accepted for publication in connection with this discussion.]

Since the time when the existence of noncellular forms of microorganisms was established, it has been found that cellular forms change into noncellular modifications as a result of exposure to unfavorable conditions.

We do not know how often noncellular modifications of pathogenic microbes are formed in the human organism, the bodies of animals, water, and other media, although this problem is of practical importance from the epidemiological standpoint. F. T. Grinbaum et al. have isolated from infected water a modified form of typhoid bacilli, but these bacilli apparently were in a cellular rather than noncellular state. At present, the epidemiological role of filterable forms of pathogenic microorganisms has not yet been clarified.

The "feeder" method, originated by V. V. Suknev 20 years ago, has been widely used in the investigation of filterable forms of bacteria. By using this method, the presence of filterable forms can be established with greater certainty than by seeding on aerated nutritive media, "microgeneration" according to Utenkov, or passing of the culture through animals. However, G. P. Kalina is of the opinion that the "feeder" microbes may have exerted an influence on the direction in which

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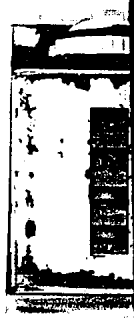

the regenerated secondary cultures have been modified. Furthermore, the microbes which serve as a "feeder" medium nourishing the filterable form may themselves develop filterable forms the regeneration of which stimulates growth of the filterable form derived from the microbe being investigated. Taking this into consideration, V. D. Timakov and Kalina proposed that suspensions of killed bacteria be used instead of live "feeder" bacteria, or else that products of the dissociation of bacteria be used.

On investigating filterable forms by the imperfect methods mentioned above, researchers obtained contradictory data.

A number of investigators (V. Y. Suknev, G. P. Kalina, V. D. Timakov, Ye. I. Zhitova, and others) have shown that the secondary culture, which has been obtained from the filterable form, differs from the initial /primary/ culture as far as the morphological, culturing, antigenic, and biochemical properties are concerned. The filterable forms are generally less active than the cellular forms from which they are derived. Modification into a filterable form represents adaptation to unfavorable conditions.

Filterable forms of cellular microorganisms propagate by forming other cellular microorganisms. Evidence to the effect that cellular microorganisms may change into viruses has not been found.

At present, it has been definitely established that abrupt qualitative changes in the biology of microorganisms take place through the medium of the formation of filterable forms. New variations and new species differing in their serological and culturing properties from those of the initial microorganisms are formed by transformation of these microorganisms into filterable modifications. This is the reason why the study of filterable forms is so important for the theory of microbiology and for practical microbiological applications in the fields of medicine, agriculture, and technology.

The necessity of solving problems that pertain to the etiology and epidemiology of typhus, typhoid, dysentery, and other infectious diseases urgently requires that the filterable forms of the causative factors of these diseases be subjected to investigation. In this connection, one may mention the results of Ye. I. Zhitova, V. M. Lavrovskaya, and N. A. Ivanova, who obtained Flexner of dysentery bacilli from the filterable form of Shiga dysentery bacilli, and bacilli of paratyphoid B from the filterable form of Flexner dysentery bacilli. One cannot avoid the conclusion that the changes in the type and species composition of dysentery bacilli which took place during the past 15-20 years are due to gradual modification of bacterial species in human organisms.

On the basis of their experimental results, V. A. Krestovnikova, V. I. Zhrubina, and N. B. Izmayleva ("Concerning the Problem of the Nature of Bacteriophage," Mikrobiologiya, Vol 21, p 721, 1952 [redacted]) regard viruses of bacteria (bacteriophages) as stages of the development of bacterial cells.

In the experiments conducted by Krestovnikova et al., rabbits were immunized by phages which are specific to strains of Proteus X_{19}, the scarlet-fever streptococcus, typhoid bacilli, and dysentery bacilli. The serums obtained in this manner were exhausted by the corresponding bacterial cultures, whereupon neutralization of the bacteriophage was attempted. The investigators found that the antiserum produced by administration of Proteus X_{19} phage is not exhausted by the bacterial culture itself, while the antiphagin contained in this antiserum is fully adsorbed by a "microculture" obtained from filterable forms of Proteus X_{19}. Similar results were obtained with the bacteriophage of the scarlet-fever streptococcus. Since the phages react with cellular cultures of bacteria rather than the filterable forms of bacteria, these results are paradoxical.

Krestovnikova's technique is open to criticism for two reasons. First, the specificity of group antigens has not been established by multiple exhaustion of the serums with two or several antigens. Second, experiments with antiserums produced by administering "microcultures" have not been conducted, so that it has not been established whether or not these antiserums are capable of neutralizing phage. Furthermore, Krestovnikova et al. obtained antiphagin by immunizing rabbits with bacterial phagolysates which, in addition to phage particles, contained immunologically active products of the lysis of bacterial cells. It should be possible to eliminate products of bacterial lysis in such experiments.

In other words, Krestovnikova and her group have not contributed anything of importance to the knowledge of the phase (literally, stage) development of bacteria. These investigators have merely brought confusion into the problem of the origin of bacteriophage and of its interrelationship with bacteria. Further confusion has been created by the announcement of the discovery of the virus of scarlet fever allegedly made by L. I. Fal'kovich, O. I. Voronkova, and R. T. Krasil'shchik at Krestovnikova's laboratory. At Ioffe's laboratory and ours, the virus isolated by Fal'kovich was proven to be identical with the virus of pneumotropic ectromelia of mice which was discovered by me in 1948. The mice which Fal'kovich used in her experiments apparently were carriers of ectromelia.

The experimental data on the basis of which Krestovnikova, Fal'kovich, and others assert that filterable forms of bacteria are identical with viruses must be regarded as invalid.

It would be of practical value to develop methods for the regeneration of filterable forms, for strengthening their antigenic characteristics, and for the stabilization of their biological properties. This would permit utilization of secondary cultures in the production of microbiological preparations. At present, one cannot mention a single instance of the practical application of a secondary culture. This is partly due to the inadequacy of the methods used in work on noncellular forms of microorganisms. In investigating filterable forms of pathogenic microbes, one should duplicate conditions which these microbes encounter in the organism. In other words, one must ensure contact of the filterable forms with living cells and with the products of the living cells' metabolism. This can be achieved by applying the method of tissue culture.

Another valuable technique is furnished by the method of cultivating filterable forms in the animal organism as described below. A small bag made of a colloidal membrane is filled with a sterile hypotonic solution of sodium chloride and a filtrate of the microbe being investigated. The bag is sewn under the skin of a newly born animal (adult animals proved unsuitable for work with the microbiological agent investigated by us). Within 3-4 days, the contents of the bag are seeded onto serum or blood agar, using serum or blood of the same species of animal.

If necessary (i.e., in cases where microcolonies do not develop in profuse quantities), the material is kept in the animal much longer or transplanted under the skin of a fresh animal. The constant circulation of nutrient substances and the ambient body temperature create conditions that are optimal for the development of the living substance of microbes. Using this method, we succeeded in regenerating cellular forms from the filterable forms of some pathogenic bacteria.

Strengthening or weakening of the properties of pathogenic microbes is achieved more readily when strict account is taken of the requirements of these microbes as far as the conditions of their existence are concerned. By taking account of these requirements, live vaccines which are effective against many bacterial and virus diseases of humans and animals have been obtained.